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PATENT SPECIFICATION

NO DRAWINGS

929,409

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Date of Application and filing Complete Specification Nov. 26, 1959.

No. 40227/59.

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Application made in United States of America (No. 781927) on Dec. 22, 1958.

Complete Specification Published June 19, 1963.

Index at acceptance:—Class 81(1), A, E1A(1B:14D), E1C(1B:14D).

International Classification:—A61j, l, n.

COMPLETE SPECIFICATION

SPECIFICATION NO. 929,409

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of THE NATIONAL CASH REGISTER COMPANY, of Dayton, Ohio, United States of America, a Corporation organised and existing under the laws of the State of Maryland United States of America.

THE PATENT OFFICE D 29663/1(15)/R.109 200 10/63 PL

sulation by liquid-liquid phase separation and to products resulting therefrom, and more particularly to a process of coacervation for encapsulating particles consisting of an oil-in-hydrophilic liquid emulsion and to the products thereof.

As employed herein, the term lipophilic is applied to those surfaces having stronger attractive forces for low dielectric constant and non-polar media than for high dielectric constant and polar media. The term hydrophilic refers to those surfaces having stronger attractive forces for high dielectric constant and polar media than for low dielectric constant and non-polar media.

According to the novel process of this invention, the novel products hereof are prepared by first forming a primary oil-in-hydrophilic liquid emulsion (the oil being a lipophilic liquid) containing one or more thickening agents as hereinafter defined in the hydrophilic liquid phase. The said primary emulsion is then dispersed in an aqueous dispersion of at least two coacervating polymers as hereinafter defined, at least one of which is a hydrophilic colloid and at least one of which is a linear macromolecular synthetic polymer, as hereinafter defined. Dilution of the resulting secondary emulsion with water, or adjustment of the pH, causes a coacervate composed of the coacervating polymers to deposit about the particles of the said secondary emulsion, these particles being composed of the primary emulsion.

single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The coacervate appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously dispersed. However, if foreign materials are present in the original dispersion, the coacervate tends to form around these materials. Technically, the term coacervation therefore relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate consists of a single polymer, the coating is termed a simple coacervate and the process is termed simple coacervation; where more than one polymer is present in the coacervate, as herein, the process is called complex coacervation and the coating is termed a complex coacervate. In this invention the materials constituting the aforesaid polymers are hydrophilic colloids and linear macromolecular synthetic polymers as hereinafter defined.

Coacervation has long been known as a phenomenon primarily of academic interest, and only in recent years has it been developed in certain limited aspects for commercial uti-

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COMPLETE SPECIFICATION

Encapsulated Emulsions and Processes for their Preparation

We, THE UPJOHN COMPANY, a Corporation organised and existing under the Laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process of encapsulation by liquid-liquid phase separation and to products resulting therefrom, and more particularly to a process of coacervation for encapsulating particles consisting of an oil-in-hydrophilic liquid emulsion and to the products thereof.

As employed herein, the term lipophilic is applied to those surfaces having stronger attractive forces for low dielectric constant and non-polar media than for high dielectric constant and polar media. The term hydrophilic refers to those surfaces having stronger attractive forces for high dielectric constant and polar media than for low dielectric constant and non-polar media.

According to the novel process of this invention, the novel products hereof are prepared by first forming a primary oil-in-hydrophilic liquid emulsion (the oil being a lipophilic liquid) containing one or more thickening agents as hereinafter defined in the hydrophilic liquid phase. The said primary emulsion is then dispersed in an aqueous dispersion of at least two coacervating polymers as hereinafter defined, at least one of which is a hydrophilic colloid and at least one of which is a linear macromolecular synthetic polymer, as hereinafter defined. Dilution of the resulting secondary emulsion with water, or adjustment of the pH, causes a coacervate composed of the coacervating polymers to deposit about the particles of the said secondary emulsion, these particles being composed of the primary emulsion.

Liquid-liquid phase separation refers to the separation of a solution or a sol of polymer or combination of polymers into two distinct liquid phases, one designated as the polymer-rich phase and the other the polymer-poor phase. Where the polymer-rich and polymer-poor phases are colloidal sols rather than true solutions, the phenomenon of phase separation is herein designated as coacervation. Thus, a coacervate is a polymer-rich sol which has separated from an original single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The coacervate appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously dispersed. However, if foreign materials are present in the original dispersion, the coacervate tends to form around these materials. Technically, the term coacervation therefore relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate consists of a single polymer, the coating is termed a simple coacervate and the process is termed simple coacervation; where more than one polymer is present in the coacervate, as herein, the process is called complex coacervation and the coating is termed a complex coacervate. In this invention the materials constituting the aforesaid polymers are hydrophilic colloids and linear macromolecular synthetic polymers as hereinafter defined.

Coacervation has long been known as a phenomenon primarily of academic interest, and only in recent years has it been developed in certain limited aspects for commercial uti-

lization. However, even with this renewed interest in the subject, the technique has been successfully described only for the coating of oil droplets *per se* and of oil droplets containing dissolved or dispersed materials. British Patent Specification No. 751,600 discloses methods for encapsulating oil droplets by coacervate coatings of the complex and simple types. Although the said patent describes the formation of coacervates from an oil-in-water emulsion, only the oil phase is actually encapsulated by the coacervate. Prior to the present invention, the encapsulation of an intact emulsion of any type by a coacervate had not been reported, and the important advantages of a coacervate-coated emulsion in which either or both of the phases thereof contain dissolved or suspended active ingredients as hereinafter specified have not been heretofore available. In addition, no method was known whereby a coacervate could be deposited on any surface, emulsion or otherwise, displaying hydrophilic qualities or being nominally hydrophilic in character, as, for example, an aqueous or a water-soluble surface.

It has now been unexpectedly found, however, that a hydrophilic surface, as, for example, an aqueous surface, presented as the external phase of an emulsion, can be adapted to receive a coacervate membrane by providing at least one thickening agent, as herein defined, in the hydrophilic liquid or aqueous external phase of the said emulsion. The presence of the thickening agent, in necessary conjunction with the oil comprising the internal phase, in some unknown manner imparts to the outer surface of the external phase the surface characteristics required for coacervate deposition. Additionally, it has been found that the class of linear macromolecular synthetic polymers can be advantageously employed as coacervating components, and that a thickening agent is useful in the hydrophilic liquid phase of the primary emulsion to fix ingredients therein.

The present process and products resulting therefrom afford a new approach to the provision of impermeable coatings of high strength or coatings which permit a gradual release of contents for water-soluble materials broadly, a problem which has heretofore resisted solution by the known techniques of coacervation. Encapsulated emulsion particles can be prepared containing appropriate active ingredients, as hereinafter specified in the emulsion phases for use as sustained release fertilizers, plant growth regulants and pesticides such as fungicides, nematocides, bactericides, viricides and the like for agricultural use. In addition, ingredients can be incorporated in premixed foods which could not normally be included because of loss in the drying step, the encapsulated ingredients being liberated by the shearing force exerted in a mixing step prior to actual use. Similarly, vitamins, notably combinations of water-soluble and oil-soluble vitamins, can be incorporated into dry cereal preparations for release in the body. Cosmetics can be prepared in which the topical agent is enclosed in impermeable but readily destructible coacervate shells. Pharmaceutical materials can be encapsulated for sustained release in the body upon contact with a predetermined pH environment or enzyme system, or where stability, odour, taste or incompatibility problems are present. Such materials can be enclosed in coatings suitable for oral, topical or injectable use by regulation of the particle size and coating thickness, permeability and hardness or by selection of coacervating components. Insecticides with selective toxicity for insects but which are relatively non-toxic toward humans can be encapsulated, for example, with coacervate coatings which are highly impermeable except in the presence of enzymes of the insects. Rodenticides which are effective on ingestion by the animals but which have odours that forewarn or repel them can likewise be coated by the method of this invention with virtually complete impermeability with respect to the odour.

Complex coacervation according to this invention involves the separation of an aqueous dispersion at least one hydrophilic colloid polymer and at least one linear macromolecular synthetic polymer as coacervating components into two phases, one of which contains the said coacervating polymers in high concentration and the other in relatively low concentration, these phases being known as the polymer-rich and the polymer-poor phases, respectively. It is essential that if one or more hydrophilic colloids are gelable, coacervation must be carried out above the gel point; if one or more are isoelectric, (by which term we mean a colloid whose molecules contain both acidic and basic groups), coacervation must be conducted at such a pH that colloids of opposite charge are present. Specifically, the term hydrophilic colloid as used herein refers to the naturally-occurring gelable and non-gelable hydrophilic colloids and derivatives thereof, examples of which are gelatin, agar-agar, albumen, alginates, deacetylated chitin, acacia, starch, and fibrinogen.

By the term "linear macromolecular synthetic polymer" we mean macromolecular polymers having an average molecular weight of at least 20,000 and having a linear, as opposed to a cross-linked, polymeric structure; for example, those whose polymeric structure comprises both lipophilic units and hydrophilic units, i.e., firstly, a recurring polymer unit which is essentially lipophilic in character and preferably comprises a single recurring group (e.g., one derived from styrene, an alkyl ring substituted styrene or an ether or ester substituted ethylene) but may also con-

tain small amounts of other groups which may be either hydrophilic or lipophilic in character, the amount of any groups of hydrophilic character being such that the polymeric recurring unit retains its essentially lipophilic character, and secondly, a recurring polymer unit which is essentially hydrophilic in character and preferably comprises one recurring group (e.g., a group derived from maleic acid, maleic acid amide, acrylic acid, crotonic acid, acrylic acid amide) but may also contain small amounts of other groups of either hydrophilic or lipophilic character, the amounts of any groups or lipophilic character being such that the recurring unit retains its essentially hydrophilic character. Examples of the groups which may be present in small amounts in either recurring unit are groups derived from acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, ethyl vinyl ether, methyl vinyl ether, vinyl chloride, and vinylidene chloride. Examples of such macromolecular synthetic polymers are the hydrolysed styrene-maleic anhydride copolymers, styrene-maleic acid amide copolymers, sulphonated polystyrenes, polymethacrylic acid, and methyl vinyl ether-maleic acid copolmer. The preferred polymers of this class are the hydrolysed styrene-maleic anhydride copolymers, the anhydride groups of which are preferably at least 50 per cent hydrolysed.

The preferred polymers of the above described type can be represented by the formula —(—R—R^1—)—$_n$ where R is a recurring unit which is comprised of groups of which at least 70 per cent are styrene residues so that R is essentially a lipophilic unit, the remaining groups comprising R being either hydrophilic or lipophilic in character, and R^1 is a recurring unit which is comprised of groups of which more than 50 per cent, and preferably more than 70 per cent, are maleic acid residues so that R^1 is essentially a hydrophilic unit, the remaining groups comprising R^1 being either hydrophilic or lipophilic in character, the said groups comprising R or R^1 which are of hydrophilic or lipophilic character being residues of ethylenic monomers such as those of acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, vinyl chloride and vinylidene chloride, the ratio of R:R^1 being from 1:1 to about 4:1 preferably from 1:1 to about 1.2:1, and n is an integer from about 90 to 1,000. The average molecular weight of the copolymer preferably ranges from about 20,000 to about 200,000.

Also included within the term "linear macromolecular synthetic polymers" are carbohydrate acetate phthalates, for example, starch acetate phthalate, cellulose acetate phthalate and acrylose acetate phthalate.

Copolymers employed in this invention are well-known in the polymer art. For example, styrene-maleic anhydride copolymer and Resin SC-2 (the latter being a modified styrene-maleic anhydride copolymer available from Monsanto Chemical Company) can be hydrolyzed to styrene-maleic acid copolymer. The hydrolysis can be partial or complete and involves a conversion of the acid anhydride linkage to α-dicarboxylic acid units. It is preferred that the hydrolysis be substantially complete, i.e., more than 50% complete.

The solubility of the polymers employed in this invention varies considerably in a selected aqueous liquid. For example, completely hydrolyzed styrene-maleic anhydride copolymer is about 2% soluble in water but at least 20% soluble in a 1:1 mixture of methanol and water. Thus, the desired amount of copolymer can be contacted with the lipophilic material at high dilutions in water or, preferably at higher concentrations, by the addition of a solubilizing agent, e.g., another hydrophilic liquid. A type of solubilizing agent useful when carboxylic acid polymers are employed are the polysaccharides, e.g., alginates, pectins, methyl cellulose, and carboxymethylcellulose. Of particular usefulness are the galactose polysaccharides, e.g., those derived from Irish moss (carrageen), e.g. that available as SeaKem Type No. 1 from Seaplant Chemical Corporation, New Bedford, Massachusetts. For example, the solubility of completely hydrolyzed styrene-maleic anhydride copolymer in water can be raised from about 2% to about 7 to 10% in the presence of relatively small amounts of this polysaccharide, e.g., one part to four parts of the copolymer. Between pH 1 and 2.5 (the pH found in a normal stomach) a styrene-maleic acid copolymer as defined herein is only 0 to 1% ionized and thus is insoluble in this pH range, making the polymer a useful enteric coating.

Ordinarily, the desired oil in hydrophilic liquid emulsion with, if desired, dissolved or suspended material in either phase thereof, is rapidly agitated with an aqueous dispersion of the coacervating polymers copolymer, e.g., in a homogenizer, or by passing through a colloid mill until the desired particle size is achieved, i.e., an average particle size of from about 0.5 to about 200 microns.

As employed herein, the term "primary emulsion" is intended to refer to the emulsion initially formed from the hydrophilic liquid, with or without dissolved or suspended ingredients, and the selected oil, with or without dissolved or suspended active ingredients. The selection of the said oil is not critical and is dependent on the function to be served by the oil, i.e., as a solvent or suspending medium or merely as the internal phase of the primary emulsion. Thus, virtually any animal, vegetable, mineral or synthetic oil having the desired physical characteristics can be employed for this purpose. Lanolin, corn oil, soybean oil, castor oil, cod liver oil and

mineral oil are examples of such oils. The conventional emulsifying agents, such as esters of polyhydric alcohols, sorbitan derivatives and sorbitan polyoxyethylene derivatives are usually employed in preparing the said primary emulsion. Selection of the particular surface active agents or combination of agents as the stabilizing agent for any particular emulsion can advantageously be made by reference to the HLB (hydrophile-lipophile balance) system, as described in Remington's Practice of Pharmacy, 11th Edition, Mack Publishing Company, 1956, page 191. Thus, by noting the HLB requirement for the particular emulsion system involved, an appropriate agent or combination of agents can be identified which will facilitate the stabilization of the desired emulsion. As with all emulsion formation problems, selection of the most suitable agents must ultimately be based on trial. Accordingly, an example of the final emulsion should be checked, for example, by diluting and agitating with a relatively large volume of water, to determine that a stable emulsion of the type desired has actually been obtained. Additionally, the selected agents must be such as not to interfere with the formation of a coacervate.

The term "hydrophilic liquid" as used herein is intended to refer to water, aqueous solutions or suspensions, and non-aqueous solutions or suspensions immiscible in the oil phase of the primary emulsion.

In addition to emulsions containing soluble or suspendable active ingredients in the hydrophilic liquid phase, the coacervates herein, by practice of the present invention, can be deposited about any emulsion containing dissolved or suspended active ingredients in the oil phase. The active ingredients to be dissolved or suspended in either the hydrophilic liquid or the oil phases are limited in selection only by the solubility, suspending characteristics or compatibility of the ingredients in both phases. As used herein, the term "active ingredients" refers to material which may be included in either or both phases of the primary emulsion and which does not substantially affect either the emulsification or coacervation processes.

The term "thickening agent" as used herein refers to materials which are substantially insoluble in the oil phase of the primary emulsion and which will cause the external phase of the primary emulsion to have a surface which is lipophilic, or, at least, less hydrophilic than water. This will permit a coacervate to deposit thereon. The presence of one or more thickening agents in the said external phase is an essential element of this invention. To be operative in facilitating coacervation, however, these thickening agents require the presence of oil in the internal phase, there being an as yet undetermined relationship or interdependence between the thickening agents and the oils. Suitable materials constituting the thickening agents hereof embrace the known natural and synthetic agents (including derivatives of both), specifically including those alluded to in Thickening Agents Used in Pharmacy, by Charles H. Becker, American Professional Pharmacist 20: 939 (October) 1954, such as acacia, tragacanth, methyl cellulose, carboxymethylcellulose and magnesium aluminum silicate, as well as other thickening agents such as the polyglycols, glycerin and syrups. The specific amounts of these materials may vary with the particular agent and system involved and can be readily determined by routine experimentation. A range of from about 1 to about 20% by weight, based on the volume of the hydrophilic liquid phase, broadly represents a practicable range, with from about 5 to about 10% being preferred in most instances. It is also often advantageous to include a thickening agent in the coacervating medium.

The term "coacervating medium" applies to the mixture of the aqueous dispersion of the coacervating polymers, with or without a thickening agent, prior to the separation of the aforesaid colloid-rich phase (coacervate).

The term "secondary emulsion" refers to the emulsion formed when the primary emulsion is added to the coacervating medium before coacervation takes place. The said secondary emulsion comprises the said primary emulsion dispersed in the coacervating medium and exists as an entity of the mixture only until a coacervate is formed about the particles of the secondary emulsion.

In the preferred embodiment of this invention, a primary oil-in-water emulsion is prepared by emulsifying (1) a vegetable oil such as corn oil into (2) approximately an equal volume of an aqueous solution containing the desired active ingredient, together with a small quantity of methyl cellulose as a thickening agent. The preparation of the emulsion is carried out at approximately 80° C. Gelatin is dispersed in water at 80° C., and styrene-maleic acid copolymer is dispersed in water and adjusted to pH 7 with 10% sodium hydroxide solution. The primary emulsion and styrene-maleic acid sol are thoroughly mixed at 80° C., and the gelatin sol is added slowly thereto with continuous stirring. The pH of the resulting mixture is lowered to 4.9 with 20% acetic acid, coacervation occurring during the acid addition. The coacervate is cooled to 5° C. to gel the gelatin component of the coacervate, which is then hardened, washed and dried.

In the preparation of the primary emulsion, the conventional emulsifying agents are normally employed to facilitate the establishment of and contribute to the stability of the primary emulsion, as well as to assure that the

correct type of emulsion, i.e., oil-in-hydrophilic liquid, is obtained. Since the size of the final encapsulated emulsion particles depends in part on the size of the emulsion droplets of the primary emulsion, the degree of dispersion of the oil in the hydrophilic liquid should be regulated in accord with the desired particle size of the ultimately obtained coacervate.

The temperature at which the primary emulsion is prepared is of little consequence with respect to the functioning of the present process. However, it is necessary that the temperature at which coacervation is carried out be above the gel point of any gelable coacervating polymer and within or closely approaching the gelling or thickening range of the thickening agent present in the hydrophilic liquid phase of the primary emulsion. Where methyl cellulose is employed as the thickening agent, the temperature of the coacervating medium should be about 80° C. to assure such an increased viscosity in the hydrophilic liquid phase. After the coacervate shell has enveloped the emulsion particles, the temperature is lowered below the gel point of any gelable component of the coacervate. Where gelatin is employed as this component, reduction in the temperature to 30° C. or lower, depending on the type of gelatin used, preferably to about 5° C., will produce the desired gelling.

For every combination of coacervating polymers there exists a pH range within which coacervation will occur. This range can be determined readily by routine experimentation in which the pH of a sample is slowly changed until a coacervate develops. It is preferable in making this determination that a trial run be conducted without an emulsion being present. The onset of coacervation can be identified by a developing cloudiness observed in the coacervating medium, and the presence of emulsion particles renders difficult the observation of the cloudiness. Where a gelable hydrophilic colloid is present as a coacervating component it is also necessary that coacervation be carried out above the gel point of the said colloid. Likewise, where the hydrophilic colloid, whether or not gelable, is an isoelectric colloid, the pH of the coacervating medium must be such that oppositely charged colloids are present therein.

Alternatively, coacervation can be induced by dilution of the coacervating medium containing the coacervating polymers with water until the operative polymer concentration range is reached. The critical concentration will vary with the particular polymers involved and can be determined by the method described above.

The ultimate particle size of the coacervate product is dependent in part, as heretofore indicated, on the degree of dispersion or size of the oil particles of the primary emulsion. In addition, the particle size is of course a function of the thickness of the coacervate coating. The more complete and rapid the mixing, the smaller the secondary emulsion droplets which are presented as nuclei about which the coacervate will form, and hence the smaller will be the final coacervate units.

Following formation of the liquid coacervate, the coacervate optionally can be gelled and hardened, plasticized or otherwise treated to adapt it to the intended use. Treating the coacervate, for example, with formaldehyde under alkaline conditions produces a hardened coacervate shell which can then be dried. For most applications, contact of the coacervate with the said formaldehyde solution for a period of about 1 to 2 hours is productive of a material having substantially improved hardness qualities over the untreated coacervate.

As either an alternative or supplementary treatment, the hardening procedure can be directed at the linear macromolecular polymeric component of the coacervate rather than at the hydrophilic colloid portion. Thus the coacervate can be subjected to dilute acetic, hydrochloric, or sulfuric acid for about 1 hour for added hardness.

Variations in the hardness of the coacervate shell can be obtained by varying the quantity of hardening agent and the period of contact therewith. Hardening likewise has considerable influence on the permeability of the coacervate, both with respect to the invasion of environmental fluids which would cause disintegration of the coating and to the containment of active ingredients which would otherwise impart undesirable color or taste characteristics to the product.

The finally treated coacervate can be separated for example by centrifuging, filtering, or decanting. This can be followed by drying by known methods, as by spray drying, freeze drying, air drying, or direct heating, optionally preceded by a washing step, to obtain a product essentially free of surface moisture. Such a product can then be formulated as a dry material.

A convenient and informative test for the integrity of a coacervate coating produced by the method of the present invention involves the incorporation of a soluble dye in the hydrophilic liquid phase of the primary emulsion. The coacervate is formed in the manner described and the resulting material, after gelling and, optionally, after hardening, is dispersed or immersed in the test liquid. The liquid can be gently stirred to thoroughly expose all coacervate surfaces. Any dye escaping from the hydrophilic liquid phase through the coacervate shell is readily detectable in the test liquid.

The following examples are illustrative of the process and products of the present in-

vention but are not to be construed as limiting the scope of the invention.

EXAMPLE 1

A suspension of 8 gm. of methyl cellulose and 50 gm. of caffeine in 100 ml. of water is heated to 80° C. One hundred milliliters of mineral oil is heated to 80° C. and emulsified into the aqueous suspension. Seventy-five grams of styrene-maleic acid copolymer is dispersed in 1500 ml. of water, heated to 80° C., and sufficient 10% sodium hydroxide is added to dissolve the copolymer. The emulsion is then dispersed in the copolymer sol with agitation. Seventy-five grams of gelatin is dispersed in 500 ml. of water, heated to 80° C., and 10% sodium hydroxide is added to raise the pH to 7. The gelatin sol is then added dropwise to the emulsion-copolymer mixture with continuous stirring. Immediately thereafter is added dropwise a sufficient amount of 20% acetic acid solution to bring the pH of the mixture down to 3.9. The material is maintained at 80° C. for 15 min., then cooled to 4° C. over a period of 30 min. To harden the coacervate 75 ml. of 37% formaldehyde solution is added, followed by the dropwise addition of 10% sodium hydroxide to bring the pH up to 8. The hardened material is then separated by centrifugation, washed with 2% hydrochloric acid and air dried.

Other thickening agents can be substituted for the methyl cellulose above in equal amounts, such as, for example, acacia, tragacanth, carboxymethylcellulose, magnesium aluminum silicate, the polyglycols, glycerin, and syrups.

Similarly, other hydrophilic colloids such as agar-agar, albumen, or fibrinogen, together with other linear macromolecular synthetic polymers such as styrene-maleic acid amide, the sulfonated polystyrenes, starch acetate phthalate, cellulose acetate phthalate, amylose acetate phthalate, polymethacrylic acid, and methylvinyl ether-maleic acid are substituted for the styrene-maleic acid above.

EXAMPLE 2

Twenty-five grams of rotenone and 2.5 gm. of magnesium aluminum silicate are dispersed in 50 ml. of water at 50° C. Fifty milliliters of corn oil is heated to 50° C. and emulsified into the aqueous suspension. A sol is prepared by dispersing 25 gm. of cellulose acetate phthalate and 25 gm. of fibrinogen in 300 ml. of water, and sufficient 10% hydrochloric acid is added to adjust the pH to 3.0. The emulsion is dispersed in the sol with vigorous agitation, and 500 ml. of water, previously heated to 50° C., is added dropwise with continuous stirring. The temperature is maintained at 50° C. for 30 min., then lowered to 4° C. over a period of 30 min. and maintained at this point for 1 hour. In order to harden the encapsulated product, 25 ml. of 37% formaldehyde solution is added dropwise, followed by a sufficient amount of 10% sodium hydroxide to raise the pH to 9.0. After the formaldehyde has remained in contact with the mixture for 1 hour, the solids are separated by centrifugation, washed with water, and spray dried at 80° C. (exhaust temperature).

EXAMPLE 3

Ten grams of carboxymethylcellulose and 1 gm. of alizarin cyanide green are dispersed in 100 ml. of water at 50° C. Fifty milliliters of peanut oil is heated to 50° C. and emulsified into the aqueous dispersion. Fifty grams of styrene-maleic acid amide copolymer is dissolved in 400 ml. of water at 50° C. and sufficient 20% acetic acid is added to adjust the pH to 3.0. Fifty grams of serum albumen is dispersed in 300 ml. of cold water, heated to 50° C., and sufficient 20% acetic acid is added to adjust the pH to 3.0. The copolymer solution is then combined with the albumen sol and the emulsion is dispersed therein with continuous agitation. Four hundred milliliters of water, previously heated to 50° C., is added dropwise to the emulsion-sol mixture. The temperature is then lowered to 4° C. over a period of 30 min. The pH of the material is then raised to 8.5 by the addition of 10% sodium carbonate solution and 50 ml. of 37% formaldehyde solution is added to harden the coating. The hardened product is separated by filtration, washed with water, and spray dried.

EXAMPLE 4

A mixture of 25 gm. of urea and 5 gm. of tragacanth is dispersed in 50 ml. of glycerin and heated to 80° C. Fifty milliliters of mineral oil is heated to 80° C. and emulsified into the glycerin dispersion. A mixture of 5 gm. of SeaKem Type No. 1 (galactose polysaccharide, Seaplant Chemical Company) and 25 gm. of styrene-maleic acid copolymer is dispersed in 500 ml. of water at 80° C. With continuous stirring, the emulsion is dispersed in the copolymer sol. A gelatin sol is made by dissolving 25 gm. of gelatin in 500 ml. of water at 80° C. The gelatin sol is added dropwise to the copolymer-emulsion mixture with continuous stirring. The temperature of the material is then lowered to 4° C. over a period of 30 min., and stirring is continued at this temperature for 1 hour. The encapsulated product is hardened by treatment with 37% formaldehyde solution for 4 hours. The hardened material is washed with water and air dried at 50° C.

WHAT WE CLAIM IS:—

1. A process for coating particles of an oil-in-hydrophilic liquid emulsion by coacervation which comprises: (1) forming a primary oil-in-hydrophilic liquid emulsion containing

at least one thickening agent as hereinbefore defined in the hydrophilic liquid phase, (2) forming a secondary emulsion comprising the said primary emulsion dispersed an aqueous dispersion of at least two coacervating polymers, at least one of which is a hydrophilic colloid and at least one of which is a linear macromolecular synthetic polymer, and (3) causing a coacervate composed of the coacervating polymers to deposit about particles composed of the primary emulsion.

2. A process as claimed in Claim 1, in which the thickening agent is acacia, tragacanth, methyl cellulose, carboxymethylcellulose, magnesium aluminium silicate, a polyglycol, glycerin or a syrup.

3. A process as claimed in Claim 1 or 2, in which the thickening agent is present in an amount from 1 to 20% by weight based on the volume of the hydrophilic liquid.

4. A process as claimed in any preceding claim, in which the hydrophilic colloid is gelable and coacervation is carried out at a temperature above the gelation point of the gelable colloid.

5. A process as claimed in any of Claims 1 to 3, in which the hydrophilic colloid is gelatin, agar-agar, albumen, an alginate, deacetylated chitin, acacia, starch, or fibrinogen.

6. A process as claimed in any preceding claim, in which the linear macromolecular synthetic polymer is a sulphonated polystyrene or a carbohydrate acetate phthalate.

7. A process as claimed in any of Claims 1 to 5, in which the linear, macromolecular, synthetic polymer has the formula:—

$$—[—R—R^1—]—_n$$

in which R is a recurring unit which is comprised of groups of which at least 70% are styrene residues so that R is essentially a lipophilic unit, and R^1 is a recurring unit which is comprised of groups of which more than 50% are maleic acid residues so that R^1 is essentially a hydrophilic unit, and in which the ratio of R to R^1 is between 1:1 and 4:1 and n is an integer from 90 to 1,000.

8. A process as claimed in Claim 7, in which the linear, macromolecular, synthetic polymer is a hydrolysed maleic anhydride copolymer, in which the anhydride groups are at least 50% hydrolysed.

9. A process as claimed in any preceding claim in which coacervation is effected by dilution with water or by a change in the pH of the system.

10. A process as claimed in any preceding claim, in which the coated emulsion particles are hardened and then separated from the solution in which they are formed.

11. A process as claimed in Claim 10, in which the coated emulsion particles are also dried.

12. A process as claimed in any preceding claim, in which the hydrophilic liquid is water.

13. A process as claimed in any preceding claim in which either or both phases of the primary oil-in-hydrophilic liquid has dissolved or suspended therein an active ingredient as hereinbefore specified.

14. A process for coating the particles of an oil-in-hydrophilic liquid emulsion substantially as described herein with reference to any of the examples.

15. A capsule comprising an oil-in-hydrophilic liquid emulsion enclosed within a complex coacervate coating, at least one coacervating component of which is a hydrophilic colloid and at least one coacervating component of which is a linear macromolecular synthetic polymer.

16. A capsule as claimed in Claim 15, in which the hydrophilic liquid is water.

17. A capsule as claimed in Claim 15 or 16, in which either or both phases of the oil-in-hydrophilic liquid emulsion has an active ingredient as hereinbefore specified dissolved or suspended therein.

18. Coated particles of an oil-in-hydrophilic liquid emulsion whenever produced by a process as claimed in any of Claims 1 to 14.

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